Optimizing the dosage of antibiotic for hospitalized pneumonia patients

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ABSTRACT

Optimizing antibiotic therapy should mean prompt achievement and maintenance of optimal exposure of the antibiotic at the site of infection, administered in a timely manner. Basic criteria to be fulfilled are: 1) does the patient really have an infection treatable by antibiotics. 2) are microbial samples warranted before starting treatment, because quantitative assessment is needed for bacteria isolated from the respiratory tract, while bacteria isolated from cerebrospinal fluid, ascites, pleural or articular aspirates are pathogens 3) mono or Combined therapy 4) which administration route? 5) duration of therapy and 6) how to prevent resistance. The interaction of antibiotic – infection site – pathogen and susceptibility –patients pathophysiology- is known as the antimicrobial therapy puzzle. PK-PD knowledge is of paramount importance. High dose, short course regiment with a once daily administration schedule for concentration dependent antibiotics e.g. levofloxacin may yield more rapid bacterial killing and prevention of resistance development, because its efficacy is related to the achievement of high Cmax / MIC ratio (>10) and AUC / MIC ratio, which for gram negative bacteria is > 100-125 and for gram positive bacteria > 30-35. Duration of antibiotic therapy can be as short as 5 days, but can also be determined by procalcitonin levels of < 0.5 mcg / ml or if it has declined > 80% of its peak level.

Keywords: *antimicrobial therapy puzzle – PK = pharmacokinetics- PD = pharmacodynamics - Cmax = maximal concentration- MIC = minimal inhibitory concentration – AUC = area undercurve–procalcitonin*

OPTIMALISASI TERAPI ANTIBIOTIK PADA PNEUMONIA RAWAT INAP

ABSTRAK

Untuk mengupayakan optimalisasi terapi antibiotik diperlukan pencapaian serta dipertahankannya konsentrasi antibiotik yang optimal ditempat infeksi pada waktu yang tepat. Kriteria dasar yang harus dipenuhi adalah 1) Apakah penderita benar benar menderita penyakit infeksi yang bisa ditanggulangi dengan antibiotika. 2) Apakah memerlukan identifikasi spesimen mikrobial untuk pemilihan antibiotika, karena infeksi saluran nafas memerlukan assesmen kwantitatif. 3) Apakan memerlukan MONO atau terapi KOMBINASI. 4) Rute administrasi lewat jalan apa ? 5) Patogen, kepekaan serta patofisioli. 6) Mencegah timbulnya resistensi. Interaksi antibiotika – situs infeksi – farmakokinetik – serta farmakodinamik amat penting dan

merupakan bagian dari TEKA TEKI terapi antibiotik (antibiotic puzzle)

Kata kunci : PK – PD – Antibiotic Puzzle - MIC

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INTRODUCTION

Optimizing antibiotic therapy should mean prompt achievement and maintenance of optimal exposure of the antibiotic at the site of infection. Questions that need to be addressed are :

- Does the patient really have an infection treatable by antibiotics?
- Are microbial samples warranted BEFORE starting therapy?
    - All bacteria isolated from cerebrospinal fluid, asci tes, pleural effusions,and articular fluid are pathogens, BUT quantitative assessment is needed for bacteria isolated from the respiratory tract.
- Mono or combined drug regiments?
- Which administration route?
- Duration of therapy
- How to prevent resistance

The WHO has issued guidelines on the Ideal drug usage in much of the same line:

The CORRECT drug, by the best ROUT, at the right DOSE, at OPTIMUM INTERVALS, for an APPROPRIATE PERIOD, based upon an ACCURATE DIAGNOSIS.

So appropiate antibiotic treatment is summarize in table 1. Implementation of this appropiate antibiotic treatment guide, brings forth the problem of the" ANTIMICROBIAL THERAPY PUZZLE" requiring knowledge of the Pharmacokinetic and Pharmacodynamic laws (figure 1)

Table 1. Appropiated Antibiotic Treatment

APPROPIATE ANTIBIOTIC TREATMENT
1) Correct choice of antibiotic on the basis a. Of the antibiogram b. Invitro bacterial susceptability 2) Timely administration a. At the right dose b.By the right route and schedule

In short, pharmacokinetic is about the dosage regimen and the serum concentration it attains, while pharmacodynamics is about the biologic effect and the drug concentration at the site of infection (figure 2)

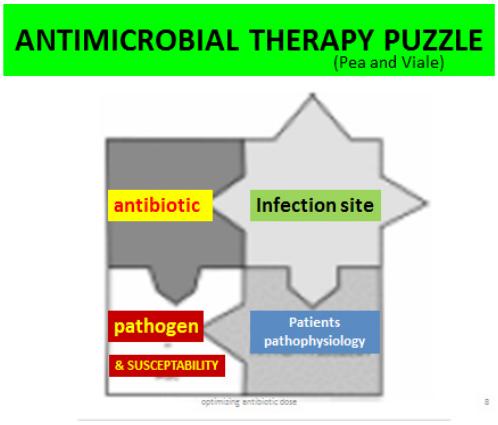

Figure 1 : Antibiotic therapy treatment

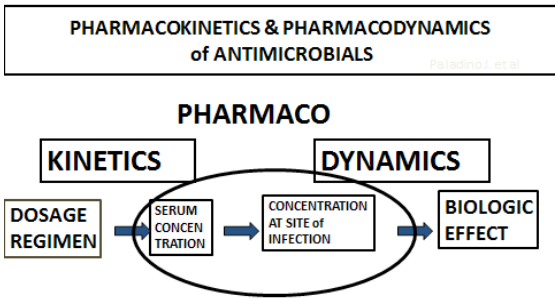

Figure 2 : PK – PD Of Antimicrobials

The anti microbial therapy puzzle reminds us of the interaction between : the antibiotic used – the infection site – the patient's pathophysiology e.g. sepsis / septic shock – and- the pathogen and its susceptability. As this topic is too broad to be covered here (see Pea and Viale), only some points relevant to this paper will be mentioned.

Antibiotic at the site of infection, depend on the diffusion profile of the drug, whether they are hydrophilic or lipophilic (table 2)

Table 2. Hydrophilic and lipophylic drugs at site of infection

THE ANTIBIOTIC AT THE SITE OF INFECTION: DIFFRENT DIFUSION PROFILE	
HYDROPHILIC	LIPOPHILIC
• MAY DIFUSE ONLY SLOWLY AND PARTIALLY IN DEEP SEATED INFECTION e.g. : – PNEUMONIA – INTRA ABDOMINAL INFECT. • NEEDING HIGHER DOSAGE TO OBTAIN OPTIMAL PD AT SITE OF INFECTION • e.g.:β-lactams, aminoglycosides, glycopeptides	• STANDARD DOSING FREQUENTLY ENSURE ADEQUAT CONC. AT INFECTION SITE • DECREASE OF Cmax AND AUC IS LESS RELEVANT • e.g.. Fluoroquinolones, macrolides, tetracyclines, chloramphenicol, rifampicin, oxazolidinones.

Patient pathophysiology, the importance of correcting hypoalbuminemia, especially when using high protein bound antibiotics e.g. teicoplanin, ertapenem, ceftriaxone. Because hypoalbuminemia results in an increase in the unbound fraction, which results greater renal clearance of the drug and less antibiotic concentration at the site of infection.

PK-PD parameters of antimicrobials devide antimicrobials into 2 broad categories; 1) concentration dependent antibiotics and time dependent antibiotics (graphically depicted at table 3 and figure 3)

Table 3. PK-PD Clinical outcome

PD ACTIVITY FL.Q AGAINST S.pneu			
	S.Pneumoniae (MIC90)	AUC(24hr) Total/FREE	AUC(24hr) / MIC 90
LEVO 500	1	48.0/33.6	34
LEVO 750	1	101.0/70.7	71
MOXI 400	0.25	33.8/17.6	70
GATI 400	0.5	33.8/27.0	54
CIPRO	2	20.2/14.1	7

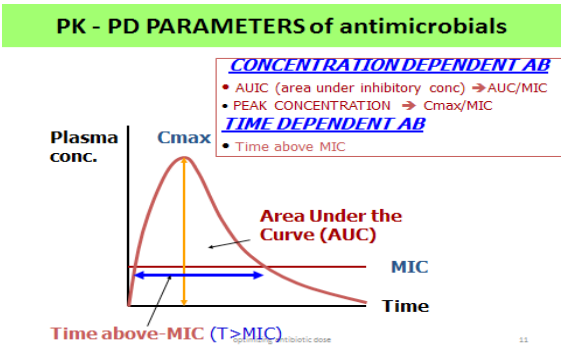

Figure 3 PK-PD parameters of antimicrobials

Table 4. Pharmacodynamics activity of Fluoro quinolones against Str.pneumoniae

PK – PD & CLINICAL OUTCOME (CRAIG W.A. PROC IDSA 39th 2001)	
ACTION	CLINICALLY EFFECTIVE
TIME DEPENDENT AB e.g.: B-LACTAMS (pen-ceph-carbapenems) MACROLIDES, TETRA, CLINDA,GLYCOPEPTIDES	TIME > MIC ➔ 40 % DOSING INTERVAL *for MAXIMUM KILL: GR (-) : T>MIC ➔ > 70 % GR (+): T>MIC ➔ > 40 %
CONCENTRATION DEPENDENT AB e.g. AMINOGLYCOSIDE QUINOLONE	AUIC (=AUC / MIC) GR (-) ve ≥ 125 GR (+) ve ≥ 30 Cmax / MIC

Table 5: The importance of rapid bactericidal killing

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optimizing antibiotic dose

Table 4, shows why Ciprofloxacine is not considered a respiratory quinolone, because its AUC/MIC ratio against Gr(=) cocci is only 7, far below the needed ratio of 30-35, resulting in less bactericidal kill and as such less clinical effectiveness and also resistance (Table 4). The simple explanation for this is that dead bugs do not mutate !!.

LEVOFLOXACINE 750 mg.

Although Paul Ehrlich's maxim of high dose, short course was coined in 1913, a century ago and meant for parasitic infections, Lala Dunbar landmark study in 2002 proved that the same holds true for high dose short course Levofloxacine in Community Acquired Pneumonia (CAP)

At this study, she showed that Levofloxacin 750 mg /OD for 5 days vs Levofloxacin 500 mg/OD for 10 days, gives quicker symptom relief (table 6), with comparable safety (table 7), while exposing the bacterial ecology to 25% less antibiotic and as such decreasing the potential for adaptive resistance.

Simple math tells us that 5 days of 750 mg = 3750 mg, while 10 days of 500 mg is 5000 mg. (Table 6, 7)

Table 6. Quicker symptom relief

QUICKER SYMPTOM RELIEF

Levofloxacin 750 mg for 5 days provides greater symtom resolution at day 3

Symptoms	n/N(%) of patients LEVO 750	LEVO 500	p[a]
Fever (patient reported)	161/239 (67.4)	130/238 (54.6)	0.006
Fever (measured)	111/226 (49.1)	89/231 (38.5)	0.027
Purulent sputum	97/239 (40.6)	73/238 (30.7)	0.059
Shortness of breath	84/239 (35.1)	66/238 (27.7)	0.132
Pleuritic chest pain	72/239 (30.1)	65/238 (27.3)	0.532
Chills	131/239 (54.8)	129/238 (54.2)	0.901
Cough	24/239 (10.0)	24/238 (10.1)	0.990

[a] p value was determined from two-sample McNemar's test.
Adapted from reference (50, 55).

Table 7. Comparable safety 750 mg OD -500 mg OD

COMPARABLE SAFETY: 750 – 500 mg

Drug-related adverse events	No. (%) of patients 750 mg q.d. for 5 days (n = 389)	500 mg q.d. for 10 days (n = 391)
Nausea	13 (3.3)	11 (2.8)
Diarrhea	7 (1.8)	9 (2.3)
Vomiting	4 (1.0)	3 (0.8)
Dizziness	4 (1.0)	2 (0.5)
Dry mouth	6 (1.5)	2 (0.5)
Dyspepsia	5 (1.3)	2 (0.5)
Abdominal pain	1 (0.3)	3 (0.8)
Genital mouliiasis	3 (0.8)	6 (1.5)

750 mg X 5 << 500 mg X 10

optimizing antibiotic dose LESS EXPENSIVE

DURATION of ANTIBIOTIC THERAPY IN CAP

There are several suggestions, but no precise guidelines, all empirical

- IDSA (Infectious diseases society of America) : 72 hrs afebrile
- Canadian infectious and thoracic Society : 1-2 wks
- BTS (British Thoracic Society) : 7-21 days, subj. to clin.judg.
- ATS (American Thoracic Society) : 7-14 days for hosp.5-7 d out pat.

Using PROCALCITONIN to customized duration of antibiotic therapy, when its concentration is less than 0.5 ng/ml or has decreased by more than 80% from its peak concentration, antibiotics can be stopped, but vigilance must be maintained to detect recurrence.

SUMMARY HIGH DOSE SHORT COURSE LEVOFLOXACIN IN CAP:

High dose, short course regimen, with a once daily administration schedule may yield

more rapid bacterial killing and prevention of resistance development, because its efficacy is related to the achievement of high Cmax / MIC ratio (>10) and auc / mic ratio, which for gram (-) bacteria should be > 100-125 and for gram (+) > 30-35

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